

**REMARKS**

After the foregoing Amendment, claims 1, 4 – 9, 18 – 20, 22 – 28, 35 – 39, 41, 43 – 45, 47 – 51, 53 – 57, 60 – 63, and 65 are pending in this application. Claim 29 is cancelled without prejudice and claim 24 is amended. Applicants submit that no new matter is introduced into the application by these amendments.

Applicants thank the Examiner for indicating that the previous 35 U.S.C. 112 rejections are overcome or withdrawn.

**Claim Rejections - 35 USC § 112, first paragraph**

The Action rejects claims 55, 56, 60 – 63 and 65 and states that these claims fail the written description requirement because the terms “scanner” and “computer” are new matter. Applicants respectfully disagree with the Action and traverse the rejection for at least the following reasons.

At page 59, lines 19-23 (Example 27), the specification states: “**Scanning** the vertical positive voltage across all vertical lines and setting a zero bias for the different horizontal lines, the conductivity of all detection sites can be monitored. Moreover, fast **scanning** techniques can be applied allowing the monitoring of 1,000,000 detection sites in seconds or less with only 1000 vertical and 1000 horizontal lines.” In Example 27, the originally filed specification states that scanning can be done to monitor conductivity when multiple detection sites are

present. The skilled artisan would readily envision that the invention described could include a scanner based on the originally filed specification.

At page 61, lines 3-5, the specification states: "The electronic multiplexing measurement allows easy control of such manipulation by, for example, **computer** control and proper software." In Example 28, which concerns quantitative measurement of the amount of a nucleic acid sequences in a sample, the originally filed specification states that a computer can be part of the invention. The skilled artisan would readily envision that the invention described could include a computer based on the originally filed specification.

Based on the foregoing, Applicants believe that the new matter rejection is improper. Applicants request withdrawal of the 35 U.S.C. § 112, first paragraph rejection of claims 55, 56, 60 – 63 and 65

**Claim Rejections - 35 USC § 102**

The Action rejects claims 1, 4 – 9, 18 – 20, 22 – 28, 45, and 57 as anticipated by WO 90/05300 (Mroczkowski). The Action states that Mroczkowski teaches a system, a method, and an assay device for assaying one or more targets in a sample, having similar characteristics to the method of the present invention. Applicants respectfully disagree with the Action and traverse the rejection for at least the following reasons.

Mroczkowski's main method involves coupling of antibodies onto gold particles, incubation of these particles with the sample including the test antigen, whereby particles coated with antibody-antigen complexes are obtained. These complex-coated particles are poured onto a diagnostic device which includes two conductive elements separated by a gap coated with the same antigen to be tested.

At page 6, the Action states that Mroczkowski's method includes a "recognition moiety positioned in the gap and bound to the substrate." In accordance with the present invention the recognition moiety, as implied by the terminology, recognizes a desired target molecule to be detected in the assay. However, in Mroczkowski's main method it is the target molecule (the antigen) that is placed onto the non-conductive substrate and not the recognition moiety (the antibody).

The Action states that Mroczkowski's method involves "determining whether the one or more targets are in the sample as a result of the extent of electric conductance between the at least two electrodes of each assay set." However, Mroczkowski teaches a competitive assay with the antigen placed on the non-conductive substrate. Mroczkowski also teaches variations of the method in which the antibody is bound to the diagnostic element and the antigen is bound to the gold particles. In both cases, however, the assay is distinguishable from the present invention as Mroczkowski described a competitive assay, namely it involves three

elements: the target molecule, a gold labeled target molecule and a probe (*e.g.*, an antigen in a sample, an antigen bound to a gold particle and an antibody). Moreover, because of their competitive nature, the degree of conductivity is in inverse relation with the amount of antigen in the sample. This is in contrast with the Action's view of Mroczkowski's method.

Several non-competitive embodiments are also provided in Mroczkowski (page 10) but they all involve use of three elements in the test, (*e.g.* an antigen, and two different antibodies), and are remote from the present invention.

The Action also states that Mroczkowski's method involves "reagents formulated to deposit a conductive substance onto a complex formed between said recognition moiety and said target." The Action points to page 15, lines 9 – 19; page 20, lines 11 – 33; page 23, lines 6 – 15; and page 25, lines 2 – 11. In these examples, however, colloidal gold (*i.e.*, gold in metal form) is attached either the target or the recognition moiety prior to Ab-Ag complex formation. In Mroczkowski, the gold particles to which the antibodies (or antigen) are originally bound form the conductive substance. Even in the non-competitive assay described, an antibody is labeled with a gold particle. Finally, Mroczkowski disclosed a silver enhancement at page 25 but the silver layer is not targeted to the complex by nucleation-center forming moieties for binding to components of the target.

Claims 4 – 9, 18 – 20, 22 – 23, and 57 depend from and include all of the elements of claim 1. With respect to claims 1, 4 – 9, 18 – 20, 22 – 23, and 57,

Mroczkowski does not disclose:

reagents formulated to deposit a conductive substance onto a complex formed between said recognition moiety and said target, wherein the reagents comprise: (i) a solution comprising nucleation-center forming entities for binding to components of said target if said target is present in the sample; and (ii) a combination of metal ions and a reducing agent to allow formation of said conductive substance on said entities, and wherein the conductive substance, when deposited onto the complex, forms a conductive bridge between the at least two electrodes of a set

as recited in independent claim 1.

Claim 45 depends from and includes all of the elements of claim 24. Mroczkowski does not disclose:

wherein the respective targets are nucleic acid molecules and the respective recognition moieties are oligonucleotides, the respective recognition moiety has a sequence which is complementary to at least a portion of the respective target

as recited in claim 24, as amended.

Mroczkowski does not disclose:

(a) reacting a sample which may or may not have targets with a first reagent solution to bind nucleation center-forming entities to said targets;

...

(d) contacting said device with a second reagent solution to form a conducting metal substance over said nucleation center-forming

entities for a time sufficient to yield a conductive bridge between said at least two electrodes

as recited in independent claim 25

Claims 27 – 28 depend from and include all of the elements of claim 26. With respect to claims 26 – 28, Mroczkowski does not disclose:

(c) contacting said device with a first reagent solution comprising monomers of a conductive polymer such that said monomers can bind to complexes formed between the targets and recognition moieties;

(d) treating said device such that said monomers will polymerize to form a conducting polymer, such that upon polymerization of the monomers a conductive bridge between the at least two electrodes of at least one set is formed,

as recited in independent claim 26.

Based on the foregoing, Mroczkowski does not disclose all of the elements of any one of claims 1, 4 – 9, 18 – 20, 22 – 28, 45, and 57 and cannot anticipate any of these claims. Applicants believe that the rejection is improper. Applicants request withdrawal of the 35 U.S.C. § 102 rejection of claims 1, 4 – 9, 18 – 20, 22 – 28, 45, and 57.

**Claim Rejections - 35 USC § 103**

***Mroczkowski and Hollis***

The Action rejects claims 29, 43 – 44, 47 – 51, 55 – 56, and 65 as obvious over Mroczkowski in view of U.S. Patent No. 5,653,939 (Hollis). Claim 29 is cancelled

an its rejection is moot. Applicants respectfully disagree with the Action and traverse the rejection for at least the following reasons.

The discussion of Mroczkowski above is incorporated herein.

Hollis teaches a system for use in connection with DNA or RNA sequencing. Hollis' system utilizes changes in electrical conductance to detect the presence or absence of a target nucleic acid in a sample; however, the method relies on the conductivity of the nucleic acids themselves, without a conductive coating. As set forth above, Mroczkowski fails to teach or suggest all of the elements of independent claims 1, 24, 25, and 26. Similarly, Mroczkowski does not disclose, teach, or suggest "reagents formulated to deposit a conductive substance onto a complex formed between said recognition moiety and said target, wherein the reagents comprise: (i) a solution comprising nucleation-center forming entities for binding to components of said target if said target is present in the sample; and (ii) a combination of metal ions and a reducing agent to allow formation of said conductive substance on said entities, and wherein the conductive substance, when deposited onto the complex, forms a conductive bridge between the at least two of the electrodes of a set," as recited in independent claim 65. Hollis does not overcome these deficiencies. Hollis fails to overcome the deficiencies of Mroczkowski and the combination fails to teach or suggest every element of any one of the rejected claims.

In contrast with the present invention, in Hollis' system the electrodes are placed in great proximity one to one another. The close spacing between the upper and lower electrodes is on the order of the length of target DNA molecule (Column 5 lines 62-64). In accordance with Hollis' system, a single DNA molecule may generate the contact between the separated conductive electrodes. Thus, the technologies of Mroczkowski and Hollis are not compatible and a person of ordinary skill in the art would not have turned to Hollis to overcome the deficiencies of Mroczkowski. Further, a person of ordinary skill in the art would not be equipped with the know-how required to arrive at the claimed system and/or method because the methods of Mroczkowski and Hollis are so substantially different from the system/method of the present invention.

Based on the foregoing, Applicants believe that the rejection over Mroczkowski in view of Hollis is improper. Applicants request withdrawal of the rejection of claims 43 – 44, 47 – 51, 55 – 56, and 65 under 35 U.S.C. § 103.

***Mroczkowski and Olsen***

The Action rejects claims 35, 37, 38, 39, and 41 as obvious over Mroczkowski in view of U.S. Patent No. 5,614,832 (Olsen). The Action states that Olsen teaches a circuit further comprising a diode or non-linear component permitting current flow through the electronic module only in the direction from the first group of



conductors to the second group of conductors. Applicants respectfully disagree with the Action and traverse the rejection for at least the following reasons.

As set forth above, Mroczkowski is deficient in teaching several elements of the claimed invention and the discussion above is incorporated herein. In particular, Mroczkowski does not teach or suggest all of the elements of claims 1 or 24, from which claims 38 and 39 depend from, respectively. Nor does Mroczkowski teach or suggest:

assay sets adapted to accept reagents formulated to deposit a conductive substance onto a complex formed between said recognition moiety and said target, wherein said reagents comprise: (i) a solution comprising nucleation-center forming entities for binding to components of said target if said target is present in the sample; and (ii) a combination of metal ions and a reducing agent to allow formation of said conductive substance on said entities;

As recited in claims 35 and 37 (or claim 41 through dependency on claim 35). The combination of Mroczkowski with Olsen fails to overcome these deficiencies and a person having ordinary skill in the art would not have arrived to the present invention by mere combination of these cited references.

Based on the foregoing, Applicants believe that the rejection of claims 35, 37, 38, 39, and 41 is improper. Applicants request withdrawal of the 35 U.S.C. § 103 rejection of claims 35, 37, 38, 39, and 41 over Mroczkowski in view of Olsen.

***Mroczkowski, Olsen, and Hollis***

The Action rejects claims 36, 53 – 54, and 60 – 63 as obvious over Mroczkowski in view of Olsen and Hollis. Applicants respectfully disagree with the Action and traverse the rejection for at least the following reasons.

Applicants' discussion of these references, above, is incorporated herein. As set forth above, Mroczkowski is deficient and combination with one or both of Olsen and Hollis fails to overcome its deficiencies. Based on the foregoing, Applicants believe that the rejection of claims 36, 53 – 54, and 60 – 63 is improper. Applicants request withdrawal of the 35 U.S.C. § 103 rejection of claims 36, 53 – 54, and 60 – 63 over Mroczkowski in view of Olsen and Hollis.

**Conclusion**

If the Examiner believes that any additional matters need to be addressed in order to place this application in condition for allowance, or that a telephone interview will help to advance the prosecution of this application, the Examiner is invited to contact the undersigned by telephone at the Examiner's convenience.

In view of the foregoing amendment and remarks, Applicants respectfully submit that the present application, including claims 1, 4 – 9, 18 – 20, 22 – 28, 35 – 39, 41, 43 – 45, 47 – 51, 53 – 57, 60 – 63, and 65, is in condition for allowance and a notice to that effect is respectfully requested.

Respectfully submitted,

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